January 28, 2004

Via fax and UPS

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 2003D-0497
Draft Guidance for Industry on Pharmacogenomic Data Submissions [Federal Register Volume 68, No. 213, Page 62461-62463, November 4, 2003]

Dear Sir/Madam:

AVENTIS appreciates the opportunity to comment on the above-referenced draft guidance entitled "Pharmacogenomic Data Submissions".

This draft guidance provides recommendations to applicants on when to submit pharmacogenomic data, what formats to submit this data in, and how the data will be used in regulatory decision making.

We acknowledge and appreciate FDA's collaboration with industry on this new guidance and offer the following comments, questions, and suggestions for your consideration.

Section I. INTRODUCTION
Page 1, Lines 23-24 – purpose of guidance

"..., and (3) how the data will be used in regulatory decision making."

Comment: unclear **how** data will be used in regulatory decision making – rather only intent of usage, VGDS or submission, is referred to in the guidance but "how" data will be actually used is not described.

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Section I. INTRODUCTION
Page 1, Lines 26-32 – PGx definition

"For the purposes of this guidance, pharmacogenomics is defined as the use of a pharmacogenomic or pharmacogenetic test (see glossary for definitions) in conjunction with drug therapy. Pharmacogenomics does not include the use of genetic or genomic techniques for the purposes of biological product characterization or quality control (e.g., cell bank characterization, bioassays). The FDA plans to provide guidance on these uses at a future time. Pharmacogenomics also does not refer to data resulting from proteomic or metabolomic techniques."

Comments:

- definitions (line 27) listed in glossary (page 15 line 586) and in Appendix E (page 26) to be reconsidered; alternates are offered below:
- alternates: 1a) use the term pharmacogenetic for all studies about DNA sequence variability, whether candidate gene or whole genome, SNP or haplotype, and 1b) use pharmacogenomic for RNA expression and proteomics (similar to CPMP position paper, CPMP/3070/01, June 4, 2002, or 2a) define pharmacogenetic tests to be tests based on SNP, DNA variants, and 2b) define pharmacogenomics test to be tests based on RNA
- unclear if usage of word "drug" (line 28) is intended to cover the following: molecule, antibody, therapeutic protein
- reference to "biological product" (line 29) to be considered for clarification to also include "biological drug product" in the list in parenthesis where cell bank, and others are listed
- reference to "metabolomic" (line 31) to be considered for revision as "metabonomic"
- proteomics (PTX) and metabonomics (line 31) will be important technologies to be used in the future and unclear if such data are fully exempt or are VGDS

Questions:

- Will this guidance be updated to cover data sources as metioned above or will that be a separate guidance, a future pharmacoproteomics or multiplexed protein analyte guidance ? For future, perhaps regional definitions might be considered, i.e., EFPIA
- What is the timeframe expectation for future guidances (lines 32-33)

Section II. BACKGROUND
Page 2-3, Lines 45, 62-63, 65-68, 79-80

"...therapy with the intent of maximizing effectiveness and minimizing risk.
Because the field of pharmacogenomics is relatively new, most experimental results may not be well enough established to be suitable for regulatory decision making.

- *Laboratory techniques and test procedures may not be well validated. In addition, test systems may vary so that results may not be consistent or generalizable across different platforms. A move to standardize assays is underway, and much more information should be available within the next several years.*

...metabolism – have well-accepted mechanistic and clinical significance and are currently being integrated into drug development decision making and clinical practice."

Comments:

- the "maximizing" phrase (line 45) to be considered for revision as "controlling and maximizing effectiveness" because this depends on whether a population level or an individual level are being referred to or considered
- in addition to information (lines 62-63) stated, there have also been very few prospective PGx or TGx (Pharmacogenomics or Toxicogenomics) trials or studies
- unclear how the standards (lines 65-68) will be defined or what will be the future decision making procedure to establish a validated test or standardized assay
- unclear if the use of "well-accepted" (lines 79 – 80) is being referred to by the Agency as a valid genetic biomarker and is the same as in line 133 on page 4 – please see comment on TMPT under Section III. A number of recommendations in this guidance are based on whether or not the use of markers is "well accepted" and this term and its usage lack meaning and clarity

Questions:

- How will IP (Intellectual Property) concerns regarding genotype/test-drug response relationships be handled ? Examples include: 1) a sponsor submitting information and then FDA requesting all other sponsors to provide same information; or 2) a sponsor demonstrating that a given gene is a "toxicity marker," and wanting to use this as a competitive advantage, and FDA being aware that another competitor drug causes change in this same gene; or 3) the commercial use and impact of one sponsor's IP by other sponsors. See additional IP comments throughout Section III.

Section III. SUBMISSION POLICY
Part A. General Principles
Page 3, Lines 128 – 145 - Biomarker Definitions

"For the purposes of this guidance, a pharmacogenomic test result may be considered a valid biomarker *if (1) it is measured in an analytical test system with well established performance characteristics and (2) there is an established scientific framework or body of evidence that elucidates the physiologic, pharmacologic, toxicologic, or clinical significance of the test results. For example, the consequences for drug metabolism of genetic variation in the human enzymes CYP450 2D6 and thiopurine methyltransferase [TMPT] are well understood in the scientific community and are reflected in certain approved drug labels. The results of genetic tests that distinguish allelic variants of these enzymes are considered valid biomarkers. The guidance makes an additional distinction between known valid biomarkers that have been accepted in the broad scientific community and probable valid biomarkers that appear to have predictive value for clinical outcomes, but may not yet be widely accepted or have been independently replicated (see Glossary). When a sponsor generates, or possesses, data sufficient to establish a significant association between pharmacogenomic test result and clinical outcomes, the test result represents a probable valid biomarker. The algorithms described below for IND, NDA, and BLA holders describe when to submit to FDA data on known valid biomarkers. Data on probable valid biomarkers need not be submitted to the IND if they are not used by the sponsor in decision making. However, we recommend that sponsors or applicants submit reports on probable valid biomarkers to unapproved NDAs or BLAs according to the algorithm in section IV.B. "*

Comments - we recommend some revisions as follows:

- Specifying definition and providing a list including what are the currently considered valid biomarkers and their usages; for example, referring to line 133 and the previous comment (lines 79-80), TMPT might be considered either as a good or as a bad example because even if it might be a valid biomarker, it is not mandatory to use it when prescribing mercaptopurins for cancer
- Identifying how a valid PGx biomarker is actually used in development, and associate it with the known (non-PGx) biomarkers; address any differences and reasons for differences, and provide examples in the guidance
- Clarifying and differentiating between the "validity" of the biomarker and the "decision making" purpose of the biomarker because interpretation regarding validity and requirement for submission might be ambiguous
- Indicating that implementation of the guidance is dependent upon regular publication of a list of FDA approved "Valid Biomarkers" ("Known" or "Probable" – might mechanism for this be via Federal Register Notices ?)
- Specifying definition of known valid biomarker, then use, and differentiating, as for valid biomarkers above
- Specifying definition of probable valid biomarker, then use, and differentiating, as for valid biomarkers above

- Specifying what is included in validation, for example validation of biomarker in a specific biological pathway, versus validation of biomarker in studying a specific compound
- Addressing validity of biomarker – also on p 18, lines 655-7, and 663. (Same as above comment on interpretation and ambiguity.)
- Addressing relevancy of biomarker to compound – also for p 13, lines 542-9
- Revising definitions also in Glossary section, p 15, lines 591-611
- Including examples of different types of valid biomarkers, also add list to line 518
- Addressing one valid biomarker versus "a group of biomarkers," use of "group," and differences between potential submission requirements, especially if only one of the biomarkers of the "group" is valid, or is used in decision making
- Including this in flow charts, p 17-20
- See comments and revised flowchart for algorithm section IV.C and Appendix C
- Including examples of different types of decision making purposes
- If definitions might not be able to be precisely revised, then only use valid biomarker and exploratory PGx data

Suggestions:
- Some other possible terminologies to be considered, such as "accepted valid biomarker," or "exploratory research" marker

Questions:
- Will FDA update guidance with new biomarkers in an Appendix format?
- Will FDA use some other mechanism to update list of biomarkers?
- Will FDA describe a transition process from probable to known valid biomarker ?
- How will the potential initial IP (Intellectual Property) of probable valid biomarkers be addressed ?

III. SUBMISSION POLICY

Part B. Specific Uses of Pharmacogenomic Data in Drug Development and Labeling
Pages 4-6, Lines 157-219, specifically lines 204-208

"In all of these cases, the FDA recommends co-development of the pharmacogenomic tests and the drug and submission of complete information on the test to the Agency (in many cases, data on the test itself may be submitted to an IDE). The FDA plans to issue further guidance on co-development of pharmacogenomic tests and drugs in the near future."

Comments:
- Companies that do not have capabilities in the development of diagnostic tools might be unfairly burdened by the recommendations in this guidance
- Concerns regarding the combined recommendations to be revised

Questions:

- Could revisions be addressed in this guidance or might a separate guidance be considered ?
- If revisions cannot be addressed, then what will the Agency do to monitor this recommendation and act accordingly ?

Section III. SUBMISSION POLICY
Part C. Voluntary Submission of Exploratory Pharmacogenomic Research Data
Page 6, Lines 223-244

"At the current time, most pharmacogenomic data are of an exploratory or research nature, and FDA regulations do not require that these data be submitted to an IND, or that complete reports be submitted to an NDA or BLA. However, to be prepared to appropriately evaluate the anticipated future submissions, FDA scientists need to develop an understanding of relevant scientific issues, such as the following.

- *The types of genetic loci or gene expression profiles being explored by the pharmaceutical industry for pharmacogenomic testing*
- *The test systems and techniques being employed*
- *The problems encountered in applying pharmacogenomic tests to drug development*
- *The ability to transmit, store, and process large amounts of complex pharmacogenomic data streams with retention of fidelity*

Therefore, the FDA is requesting that sponsors conducting such programs consider providing pharmacogenomic data to the Agency voluntarily, when such data are not otherwise required under IND and NDA or BLA regulations. Voluntary Genomic Data Submissions (VGDSs) can be used for the submission of pharmacogenomic studies that are not required to be submitted. The FDA will establish a cross-center Interdisciplinary Pharmacogenomic Review Group (IPRG) to review VGDSs, to work on ongoing policy development, and to advise review divisions dealing with pharmacogenomic data."

Comments - we recommend some revisions for the *regulatory submission requirements* as follows:

- Data format for VGDS – Specify preclinical and clinical requirements
- General format of VGDS – Address or provide some alternate examples
- Benefit of VGDS – Include example of PGx data with no or limited utility to demonstrate FDA's position when a VGDS is not warranted
- Submission of VGDS – Specify FDA filing system process
- Confidentiality of VGDS – Include example where IND not yet submitted
- IP associated with VGDS – Include and address clarification on IP (Intellectual Property)
- FDS (full data submission) format – Electronic, CTD, other ?
- For preclinical data, recommend format such as developed by ILSI/HESI (MIAME/Tox)
- FDS content – Data Synopsis, Summaries, Raw, etc.

Questions:

- In case an IND has not yet been opened, will the Agency be agreeable to provide feedback on VGDS ?
- If the Agency is agreeable, then how and what will the feedback process be ?

Comments - we recommend some additions to the *regulatory processes* as follows:

- Include FDA consultation choices regarding PGx – Meeting types (A, B, C)
- Include how VGDS and/or FDS will be reviewed, including but not limited to the correlation between different statistical methodologies
- Include how IP of genetic loci might be protected and in same phrase specify statement by adding candidate genes or whole genome scans
- Include how resolution will be addressed if sponsor does not perform a genetic test for a specific trial for which the Agency expects a genetic test
- Include how Reviewing Division and IPRG will meet with sponsor, or plans for interaction between IPRG, sponsor, and Reviewing Division
- Include IPRG composition, expectations, and processes
- Specify IPRG role regarding ethics, confidentiality, authority
- Include FDA mechanism to coordinate IPRG and Reviewing Division requirements / expectations
- Consider and develop processes for sponsors to submit information to the IPRG for seeking advice
- Include how IPRG process will be linked with potential future ICH processes, especially considering the developing discussions for the need of an ICH working group
- Address coordination of this guidance with other developing guidances, policies, and position papers in the US and ex-US

Also see Section V.

Section IV. SUBMISSION OF PHARMACOGENOMIC DATA
Part A. Submission to an Approved NDA or BLA
Pages 6-8, Lines 253-314

"Section 312.23 outlines information submission requirements for an IND, including for data generated or available during the IND phase. Section 312.23(a)(8) lays out the requirements for pharmacology and toxicology information: "Adequate information about pharmacologic and toxicological studies of the drug involving laboratory animals or in vitro, on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations" (emphasis added). The in vitro and animal studies needed to establish a basis for proceeding with human trials of various types are well established internationally. Therefore, pharmacogenomic data relevant to, or derived from, animal or in vitro studies should ordinarily be submitted under § 312.23(a)(8) when the sponsor wishes to use these data to make a scientific case, or when the test is well established as a predictive biomarker (i.e., is a known valid biomarker).
//
Data from a VGDS submission to an IND will not be used for regulatory decision making. However, after the sponsor submits a VGDS, if additional information becomes available that renders the results required to be submitted under §§ 312, 314, or 601, the sponsor must submit the data to the IND, NDA, or BLA, respectively, and should follow the appropriate algorithm."

Comments:
- Line 262 – remove "…, or when the test is well established…..biomarker."
- Line 273 – usefulness of PGx data for regulatory decision making if PGx data or PGx test is not well established
- Line 289 – the valid biomarker must have some relevance for the assessment of safety or efficacy in humans or safety in animals for the compound before having to be submitted – same for Appendices
- Line 300 – DNA variations are not only SNPs
- See Power point slide in Appendix C.

Section IV. SUBMISSION OF PHARMACOGENOMIC DATA
Part B. Submission of Pharmacogenomic Data to a New NDA or BLA
Pages 6-8, Lines 318-378

"Section 314.50 outlines the NDA submission requirements; section 601.2 generally outlines BLA submission requirements. As the introduction to § 314.50 states, "the

[NDA] application is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug product pertinent to an evaluation of the application that is received or otherwise obtained by the applicant from any source." Therefore, to comply with these regulations, sponsors will need to provide reports of pharmacogenomic investigations in their NDAs, and to permit a thorough analysis of a biologics application, a sponsor would want to submit such a report in its BLA. However, the extent and format of such reports will depend on the relevance and application of the information.
//
See Appendix B for additional guidance on how to assess whether to submit pharmacogenomic data to an unapproved NDA or BLA."

Comments:

- Line 346 – replace "complete data" with "a list of genes used for the assessment and final interpretation."
- Line 363 – the probable valid biomarker must have some relevance for the assessment of safety or efficacy in humans or safety in animals for the compound before having to be submitted – same for Appendices
- Line 368 – remove "detailed"
- Line 372 – remove "…the submission requirements…of the study." And replace with "…no submission is necessary."

Section IV. SUBMISSION OF PHARMACOGENOMIC DATA
Part C. Submission to an Approved NDA or BLA
Pages 9-10, Lines 382-389

"The requirements for submitting new scientific information to an approved NDA or BLA are outlined in §§ 314.81(b)(2) and 601.12. Results of nonclinical or clinical pharmacogenomic investigations on known or probable valid biomarkers must be submitted in the annual report as synopses or abbreviated reports (21 CFR 314.81(b)(2)).

Pharmacogenomic study results of other types do not meet the submission requirements outlined in the regulations (§ 314.81(b)(2)). However, such reports can be voluntarily submitted to the NDA or BLA as a VGDS."

Comment: addition of supplemental filing to be added to draft guidance

- Address submission algorithm for an approved NDA, BLA, or Supplement
- Revise Appendix C – Please see revised slide inserted under Appendix C

Section IV. SUBMISSION OF PHARMACOGENOMIC DATA
Part D. Compliance with 21 CFR Part 58
Page 10 Lines 393-405

"Questions have been raised about the need for pharmacogenomic studies to comply with the requirements of 21 CFR part 58, which describes good laboratory practices (GLPs) for nonclinical laboratory studies that support INDs and NDAs. Section 58.3(d) (21 CFR 58.3(d)) defines nonclinical laboratory studies as "in vivo or in vitro experiments in which test articles are studied prospectively in test systems under laboratory conditions to determine their safety. The term does not include studies utilizing human subjects or clinical studies or field trials in animals. The term does not include basic exploratory studies carried out to determine whether a test article has any potential utility...."

The requirements of part 58 apply to nonclinical studies submitted to support safety findings, including nonclinical pharmacogenomic studies intended to support regulatory decision making. Any studies eligible to be submitted in an abbreviated report, synopsis or VGDS under the algorithms discussed above do not fall under part 58."

Comment:

- Include in guidance that exploratory gene expression analysis can be done in GLP studies and GLP requirement not applicable to the gene expression work
- Modify part 58 to indicate that exploratory work can be done in GLP studies as long as protocol clearly indicate what is exploratory and what is not. This option would support potential future development in metabonomics, proteomics, and others.

Section V. FORMAT AND CONTENT OF A VGDS
Page 10-12, Lines 410-470

"This section provides recommendations on the format and content of VGDS reports and data. The FDA invites submission of exploratory pharmacogenomic data on drugs or candidate drugs whether or not the drugs are currently the subject of an active IND, NDA, or BLA. Exploratory genomic data may result from, for example, DNA microarray gene expression profiling experiments, expression biomarkers from single or limited gene expression profiles, genotyping or single-nucleotide polymorphism (SNP) profiling of clinical study participants, or from other studies using evolving methodologies that are intended to facilitate global analysis of gene structure or gene function.
//
The Agency will develop more specific guidance on how to submit detailed reports of genomic research data to INDs, NDAs, and BLAs."

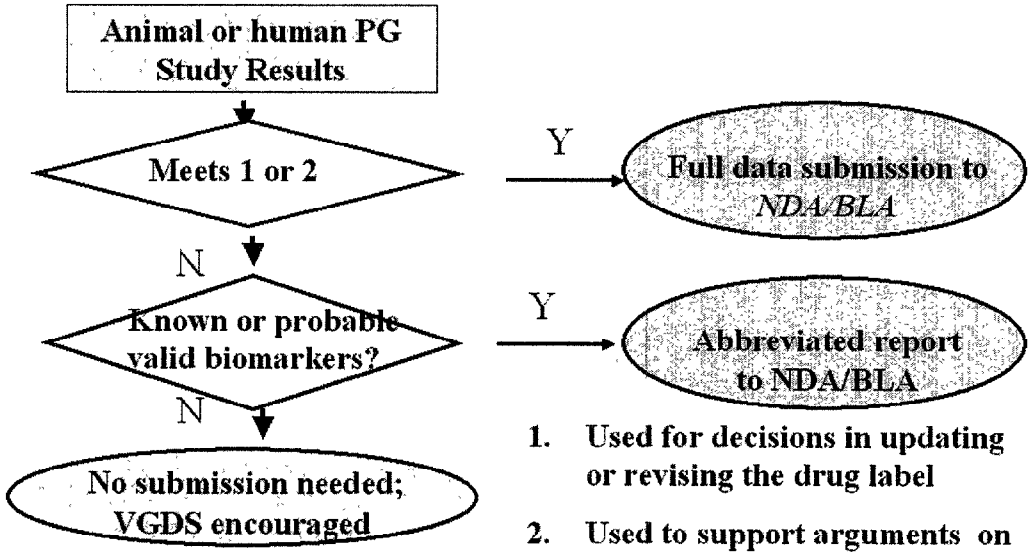
Comments:

- Include some current programs the Agency is working with to elucidate exploratory genomic data
- Lines 427-468 – seem to favor expression; reporting SNP analysis might be simpler and a VGDS format could be included
- Overall, also see Section III, Part C comments

Appendix C
Page 21

Suggested revised slide inserted below:

Submission of Data to an approved NDA or BLA or supplement



1. **Used for decisions in updating or revising the drug label**
2. **Used to support arguments on post-marketing surveillance**
3. **Is a *known valid biomarker* or a probable valid biomarker**

See also Section IV comment.

Appendix D
Page 22-25

Comment: sections in Appendix D would benefit from examples when submission to the Agency would NOT be encouraged; examples providing considerations with respect to quality or significance of submission might be considered.

On behalf of Aventis we truly appreciate the opportunity to comment on the Draft Guidance for Industry on Pharmacogenomic Data Submissions and are much obliged for your consideration.

Sincerely,

Steve Caffé, M.D.
Vice President, Head US Regulatory Affairs